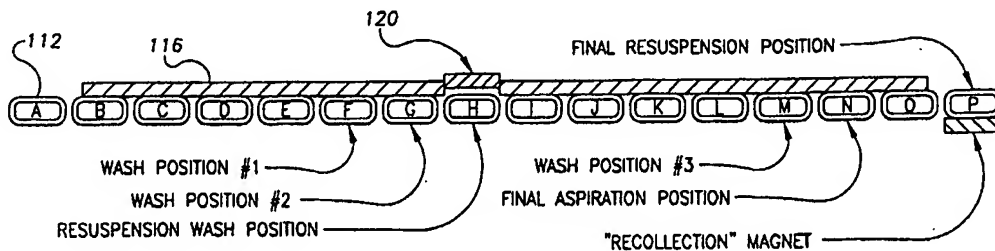


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(54) Title: **METHOD AND APPARATUS FOR WASH, RESUSPENSION, RECOLLECTION AND LOCALIZATION OF MAGNETIZABLE PARTICLES IN ASSAYS USING MAGNETIC SEPARATION TECHNOLOGY**

**(57) Abstract**

Method and apparatus for enabling resuspension wash and magnetic localization of sample components bound to particles with magnetic properties in reaction vessels during separation and wash for enhanced chemiluminescent signal generation in biomedical assays. The assays involve moving reaction vessels past magnets that partially localize the particles prior to passing a reduced strength magnet where washing occurs, with or without resuspension, after separating out the unbound particles and liquid. The band of particles is subsequently resuspended in acid for chemiluminescent purposes. A variety of magnet configurations are employed to realize the reduced strength magnet. Reduced strength magnets adjacent the full width magnets prevent the band of magnetic particles from becoming split. The localized particles enable more efficient resuspension by reagent.

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6 Method and Apparatus for Wash, Resuspension, Recollection
7 and Localization of Magnetizable Particles in Assays
8 Using Magnetic Separation Technology
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12 RELATED APPLICATIONS

13 This application is a continuation-in-part of U.S.
14 Patent Application No. 08/644,909, filed May 10, 1996.
15

16 FIELD OF THE INVENTION

17 The invention generally relates to the field of
18 biomedical assays employing magnetic separation techniques,
19 and specifically to a method and apparatus for focusing or
20 localizing magnetizable particles during separation and wash
21 in such assays.
22

23 BACKGROUND OF THE INVENTION

24 Heterogeneous immunoassays typically require the
25 separation of sought-for components bound to component-
26 selective particles from unbound or free components of the
27 assay. To increase the efficiency of this separation, many
28 assays wash the solid phase (the bound component) of the
29 assay after the initial separation (the removal or aspiration
30 of the liquid phase). Some chemiluminescent immunoassays use
31 magnetic separation to remove the unbound assay components
32 from the reaction vessel prior to addition of a reagent used
33 in producing chemiluminescence or the detectable signal
34 indicative of the amount of bound component present. This is
35 accomplished by using magnetizable particles including, but
36 not restricted to, paramagnetic particles, superparamagnetic
37 particles, ferromagnetic particles and ferrimagnetic

1 particles. Tested-for assay components are bound to
2 component-specific sites on magnetizable particles during the
3 course of the assay. The associated magnetizable particles
4 are attracted to magnets for retention in the reaction vessel
5 while the liquid phase, containing unbound components, is
6 aspirated from the reaction vessel.

7 Washing of the solid phase after the initial separation
8 is accomplished by dispensing and then aspirating a wash
9 solution, such as de-ionized water or a wash buffer, while
10 the magnetizable particles are attracted to the magnet.

11 Greater efficiency in washing is accomplished by moving
12 the reaction vessels along a magnet array having a gap in the
13 array structure proximate a wash position, allowing the
14 magnetizable particles to resuspend during the dispense of
15 the wash solution. This is known as resuspension wash.
16 Subsequent positions in the array include magnets, allowing
17 the magnetizable particles to recollect prior to aspiration
18 of the wash solution and introduction of reagent beyond the
19 end of the magnet array.

20 Prior art wash block configurations have employed iron-
21 based or non-iron-based inserts in the gap of the magnet
22 array at the wash position. Rather than simply removing a
23 magnet from the resuspension position, the insert is intended
24 to maintain the accumulation of magnetic particles in the
25 absence of resuspension wash, and to orient these particles
26 for thorough resuspension if resuspension wash is employed.
27 In addition, the insert prevents a reaction vessel from
28 becoming misaligned and jammed in the magnet array. While
29 functioning adequately for assays which employ resuspension
30 wash, it is evident that the provision of such inserts in
31 place of a magnet at the wash position adversely affects
32 assays which do not use the resuspension in washing but which
33 proceed through the wash position without resuspension. With
34 a non-iron-based insert such as of aluminum or ceramic, a
35 single band of magnetizable particles which is normally
36 formed along the interior of the reaction vessel as it passes
37 the magnet array, during the initial separation, is split

1 into two smaller bands on either side of the reaction vessel
2 due to attraction by the magnets on either side of the insert
3 at the resuspension and wash position. This is due to the
4 minimal effect by the insert on the magnetic flux patterns.
5 Since reagent is introduced into the reaction vessel in a
6 stream directed toward where the magnetizable particles
7 collected before splitting, the split in the banding of the
8 magnetizable particles results in the stream missing the main
9 concentration of magnetizable particles. Poor resuspension
10 of the magnetizable particles during resuspension wash and
11 upon addition of an acid reagent used to condition the bound
12 component reagent in the generation of a chemiluminescent
13 signal results.

14 Similarly, the use of an iron-based insert such as of
15 steel may result in split-banding of the magnetic particles,
16 but may further introduce a band of particles in the middle
17 of the cuvette wall adjacent the insert. This is due to the
18 tendency of an iron-based insert to shunt magnetic fields.
19 While the formation of a band or pellet of particles in the
20 middle of the cuvette wall is desired, the reproducibility of
21 this response across varying assays for a single iron-based
22 insert configuration is unlikely. This is due to the varying
23 characteristics of the assays, including concentration of
24 surfactants and the particle masses.

25 Other prior art approaches for facilitating resuspension
26 wash have employed inserts of reduced width with the
27 intention that magnetic fields extending from the adjacent
28 magnets will hold the magnetic particles in position.
29 However, this approach has also resulted in the split-banding
30 of the particles.

31 Therefore, the prior art fails to provide a wash region
32 which enables the efficient washing of magnetizable particles
33 during the wash phase of a magnetic separation assay without
34 adversely effecting assays not employing resuspension wash.

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1 SUMMARY OF THE INVENTION

2 It is an object of the present invention to provide
3 methods and apparatus for focusing or localizing magnetizable
4 particles during separation and wash for enhanced signal
5 generation in assays which use magnetic separation
6 technology. It is a further object of the present invention
7 to provide a wash region enabling enhanced suspension of
8 solid phase components for a sample, regardless of whether it
9 undergoes resuspension wash.

10 These objects are achieved by employing an insert of
11 soft magnetic material in place of separation magnets at a
12 wash position in the array, wherein the insert has a width
13 greater than the width of a reaction vessel passing thereby.

14 Further, the magnets of the array both up and downstream of
15 the wash position terminate at locations intermediate to the
16 reaction vessel for enhanced focusing of magnetizable
17 particles in the path of a reagent stream, resulting in
18 improved resuspension of the magnetizable particles by the
19 reagent. Therefore, resuspension wash efficiency is
20 enhanced, and magnetizable particle focusing is increased,
21 leading to a more efficient magnetizable particle
22 resuspension for the signal generation portion of the assay.

23 At the end of the magnet array, a focusing magnet having
24 a face dimension less than a vessel width is employed in the
25 array to more completely localize the magnetizable particles
26 prior to being in the path of an injected acid stream
27 employed to initiate the reaction leading to
28 chemiluminescence.

29 For assays not employing resuspension wash, the
30 provision of the soft magnetic insert results in avoidance of
31 split banding of the magnetizable particles, while
32 magnetizable particle focusing results in improved
33 chemiluminescent reaction.

34 For assays employing resuspension wash, the soft
35 magnetic insert enables resuspension wash while avoiding
36 premature collection and splitting of magnetizable particles
37 due to the influence of magnets adjacent to the wash

1 position. As with assays not employing resuspension wash,
2 magnetizable particle focusing results in improved
3 chemiluminescent reaction.

4 It is a further object of the present invention to
5 provide a wash region which enables the accurate and
6 predictable collection of magnetizable particles, whether or
7 not resuspension wash is performed at that region.

8 This object is achieved, in an alternative embodiment,
9 through the provision of a magnet of reduced strength,
10 relative to the other magnets in the array, at the wash
11 position. For instance, in a preferred embodiment, the
12 reduced strength magnet provides a magnetic field at the
13 respective reaction vessel position one-half that as provided
14 by the other magnets. This reduced strength magnet acts as a
15 replacement for the soft magnetic insert previously
16 mentioned, which, on its own, provides no magnetic field.
17 Additionally, the magnets of the array which are disposed at
18 reaction vessel positions before and after the wash position
19 are not trimmed, but instead extend across the full extent of
20 the respective reaction vessel position. At the last
21 reaction vessel position in the array, the respective magnet
22 is disposed on a side of the reaction vessel opposite that of
23 all previous magnets in order to avoid the dense packing in
24 collected particles which sometimes results in incomplete
25 resuspension in the stream of final reagent. A further
26 feature of this alternative embodiment includes lowering the
27 focal point of the magnetic field, generated by magnets of
28 the array, at a reaction vessel position immediately
29 following the reaction vessel position having the reduced
30 strength magnet proximate thereto.

31

32 BRIEF DESCRIPTION OF THE DRAWINGS

33 This invention is pointed out with particularity in the
34 appended claims. The above and further advantages may be
35 more fully understood by referring to the following
36 description and accompanying drawings of which:

1 Fig. 1A is an elevation view of a magnet array and a
2 sequence of reaction vessels passing therethrough according
3 to the present invention;

4 Fig. 1B is an elevation view of the magnet array of Fig.
5 1A in which resuspension wash is performed;

6 Fig. 2 is an elevation view of the magnet array of Fig.
7 1A illustrating a reaction vessel transport mechanism;

8 Fig. 3 is a rear elevation view of the magnet array of
9 Fig. 1A illustrating a magnet array support structure;

Fig. 4A is a side elevation view of a non-resuspension wash nozzle oriented proximate a reaction vessel for use in the magnet array of Fig. 1A;

13 Fig. 4B is a side elevation view of a resuspension wash
14 nozzle oriented proximate a reaction vessel for use in the
15 magnet array of Fig. 1B;

16 Fig. 5A is an elevation view of a magnet array and a
17 sequence of reaction vessels passing therethrough according
18 to a further embodiment of the present invention;

19 Fig. 5B is an elevation view of the magnet array of Fig.
20 5A in which resuspension wash is performed; and

21 Fig. 6 is a top view of the magnet array of Fig. 5A.

23 DETAILED DESCRIPTION

24 To increase the efficiency of the separation of bound
25 components from free components in immunoassays, many assays
26 wash the solid phase (bound component) of the assay after the
27 initial separation (removal of the liquid phase and unbound
28 component). The present invention operates in the context of
29 a chemiluminescent immunoassay of known type which uses
30 magnetic separation to remove unbound assay components from a
31 reaction vessel such as a cuvette.

32 The presently disclosed method and apparatus enables a
33 resuspension wash of magnetizable particles with improved
34 wash efficiency and focuses magnetizable particles from a
35 band to a small region or dot, enabling a more efficient
36 resuspension of magnetizable particles for a signal
37 generation portion of the assay.

1 In all of the following discussions, it is assumed that
2 the reaction vessels progress from the left-hand side of the
3 illustrations to the right-hand side past a fixed magnet
4 array at regularly timed intervals, although continuous
5 motion is not excluded. Means for imparting lateral
6 translation of the reaction vessels is described subsequently
7 with regard to Fig. 2. In an exemplary embodiment, such
8 interval is approximately 15 seconds. Additionally,
9 throughout this description, aspiration and dispense
10 functions are executed via means known in the art without
11 full details being shown.

12 The magnet array of Figs. 1A and 1B includes a
13 succession of reaction vessels such as cuvettes 12, each
14 containing assay components and magnetizable particles 14
15 which are initially in a freely distributed state within the
16 respective cuvette 12. The concentration of solid phase
17 (bound component) of the assay remaining in free suspension
18 in the cuvette at position B is less than that of the first
19 cuvette 12 in position A due to the initial collection of
20 solid phase proximate magnets of the array 16 at position B.

21 In the cuvette 12 of position C, this effect is more
22 evident. By the time a cuvette has progressed to position D,
23 the majority of the solid phase 14 has collected proximate
24 respective magnets of the array 16.

25 References to "magnets" adjacent a respective position
26 are understood to refer to a pair of adjacent magnets of
27 oppositely oriented polarity, one above the other, proximate
28 the respective cuvette position. A band of magnetizable
29 particles 14 forms along the junction of these two magnets,
30 where the magnetic gradient is at a maximum.

31 Non-resuspension washes are provided at positions F, G,
32 and M in the illustrative embodiment of Fig. 1A, and at
33 positions F and M in the embodiment of Fig. 1B. At these
34 positions, liquid phase is aspirated from the cuvette 12 via
35 tubes (15, 17, 19 in Fig. 1A and 15, 19 in Fig. 1B) and wash
36 solution is reintroduced via nozzles (30, 32, 34 in Fig. 1A
37 and 30, 34 in Fig. 1B). The nozzles are positioned in front

1 of respective tubes in the view of Figs. 1A and 1B. In
2 particular, the nozzles are angled toward the front of the
3 respective cuvette 12 (out of the page in Figs. 1A and 1B) to
4 avoid disturbing the pellet of solid phase 14 collected at
5 the respective magnets of the array 16.

6 The tube 21 at position N of Figs. 1A and 1B is employed
7 to aspirate liquid phase from the respective cuvette 12 prior
8 to the introduction, at position P, of reagent via nozzle 36,
9 the reagent facilitating a subsequent chemiluminescent
10 reaction within a luminometer. In contrast to the non-
11 resuspension wash nozzles (30, 32, 34 in Fig. 1A and 30, 34
12 in Fig. 1B), the reagent dispensing nozzles 36 are angled
13 toward the pellet of solid phase 14 in order to thoroughly
14 disperse it.

15 In prior art magnet arrays, a portion of the liquid
16 phase may remain trapped within the solid phase 14 prior to
17 introduction of the reagent at position P, even after
18 repeated non-resuspension washes, such as at positions F, G,
19 and M in Fig. 1A and positions F and M in Fig. 1B. This
20 trapped liquid phase limits the accuracy of the assay.

21 At position K of Fig. 1A, the magnets of the array 16
22 proximate the cuvettes 12 are disposed at a lower position.
23 This provides the solid phase pellet 14 with time to
24 recollect at the lower position prior to the introduction of
25 assay reagent at position P. Thus, when reagent is directed
26 at the pellet 14 in position P by the nozzle 36, the solid
27 phase 14 will be centrally located in the reaction vessel 12
28 when the acid is applied at position P. However, such
29 repositioning of the pellet does not necessarily enhance the
30 ability of the non-resuspension washes to rid the solid phase
31 14 of trapped liquid phase.

32 In Fig. 1A, a resuspension wash is not employed, and as
33 such the focused, or localized, solid phase remains proximate
34 respective magnets 16 as the cuvette 12 progresses through
35 the wash block.

36 In contrast, the magnet array of Fig. 1B does employ a
37 resuspension wash. Resuspension washing of the solid phase

1 involves the aspiration of the liquid phase containing the
2 unbound components of the assay from the cuvette 12 at
3 position G via the tube 17 while the bound components are
4 held in place by respective magnets in the array 16. This is
5 followed by re-introduction of wash solution into the cuvette
6 12 at position H by a dispense nozzle 32 angled at the solid
7 phase pellet 14 collected at the back of the cuvette 12
8 proximate the magnets 16.

9 At position H, magnets of the array 16 have been
10 replaced by a soft magnetic insert 20. By dispensing wash
11 solution onto the magnetizable particles via the nozzle 32 in
12 the absence of magnets in the array 16, the magnetizable
13 particles are resuspended, exposing more surface area, and
14 freeing liquid phase trapped during initial magnetizable
15 particle collection. After the solid phase has been
16 resuspended, it is recollected by a subsequent series of
17 magnets in the array 16 at positions I *et seq.* prior to
18 aspiration of the wash solution and introduction of the acid
19 reagent at position P. Other wash stages, in addition to
20 those illustrated, are possible.

21 The wash block of Figs. 1A and 1B is provided with a
22 large gap in the magnet array at position H, thus enhancing
23 resuspension wash. Prior art magnet arrays employed narrower
24 gaps, resulting in split bands of magnetizable particles due
25 to the attractive forces of array magnets on either side of
26 the narrow gap.

27 The present invention avoids the splitting of the solid
28 phase material into bands at opposite sides of the cuvette
29 12, in part, by providing a focusing of the solid phase 14
30 into a smaller band or dot 24. The gap at the resuspension
31 wash position is filled with an insert 20 made of a soft
32 magnetic material such as low carbon steel. Further, the
33 magnets of the array 16 at positions G and I on either side
34 of the resuspension wash position, position H, are trimmed
35 such that the gap in the array of magnets 16 and the insert
36 20 extend proximate a region of the reaction vessels 12

1 previously occupied by the solid phase band 14 adjacent to
2 the resuspension wash position.

3 As a result, magnetizable particles linearly banded by
4 the magnets in the previous positions, but which are no
5 longer directly aligned with magnets of the array 16, migrate
6 along the reaction vessel 12 walls towards portions of the
7 reaction vessel interior proximate the trimmed magnets 16.
8 For instance, in position G, the magnets 16 are trimmed on
9 the right-hand side. Magnetizable particles formerly aligned
10 in the trimmed region now migrate to the center of the vessel
11 12, over the trimmed magnets 16.

12 The magnetizable particle banding pattern in the
13 reaction vessel at the resuspension wash position, position
14 H, remains unchanged in the absence of resuspension wash
15 (Fig. 1A). With resuspension wash (Fig. 1B), the large soft
16 magnetic insert 20 enables the complete resuspension of the
17 solid phase 14 free of influence of magnets at positions G
18 and I. Also, the provision of magnets trimmed on a left-hand
19 side at position I downstream of the resuspension wash
20 position, position H, further serves to avoid influencing the
21 magnetizable particles during the resuspension wash in Fig.
22 1B.

23 The array 16 magnets at position I, downstream of the
24 resuspension wash position, position H, and the soft magnetic
25 insert 20, is also trimmed on its left-hand side in Fig. 1A.

26 This serves to focus the solid phase 14 downstream of the
27 resuspension wash position, position H. The magnetizable
28 particles on the left side of the reaction vessel 12 are no
29 longer directly aligned with magnets 16 at position I.
30 Rather, they migrate toward the right, into the center of the
31 vessel 12. The net effect is a conversion of the
32 magnetizable particles from a wide band 14 to a more compact,
33 centrally located band 26.

34 For the embodiment of Fig. 1A, the single magnetizable
35 particle band at position H does not split into two bands as
36 in the prior art because the soft magnetic insert 20 acts to
37 short out, or minimize, the magnitude of the field gradient

1 in the resuspension wash position, position H, and because
2 trimming the magnets of the array 16 at positions G and I
3 reduces the reach of the fields, from the same, into the
4 resuspension position H.

5 At position M, trimmed magnets 27 are provided to
6 further narrow the band of collected magnetizable particles.

7 In a further embodiment, even smaller magnets 28, focusing
8 magnets, are employed at position N to focus the magnetizable
9 particles into yet a smaller area, thus providing a smaller
10 target of solid phase 24 at position P for more efficient
11 resuspension upon dispense of reagent. Smaller, focusing
12 magnets 28 are not used in a preferred embodiment for the
13 initial collection of the solid phase because, amongst other
14 things, the larger the magnet surface area, the faster the
15 collection of the magnetizable particles.

16 In an alternative embodiment, all of the magnets in the
17 array 16 along the length of the wash block are provided as
18 focusing magnets 28, though the resuspension wash position,
19 position H, would continue to be provided with a gap such as
20 that provided by the soft magnetic block 20 of Figs. 1A and
21 1B. However, such an embodiment would require more time for
22 each reaction vessel 12 to be proximate the magnets 28 in the
23 array to provide an equivalent degree of capture capability
24 due to the smaller size of the magnets in such an embodiment.

25 In yet another embodiment of the present invention, it
26 is possible to enable further focusing of the magnetizable
27 particles by employing another gap in the magnet array 16
28 prior to the focusing magnets 28 at position N. For
29 instance, such a gap could be employed at position L. Here,
30 the magnetizable particles 14 have already been gathered at
31 an interior wall of the reaction vessel 12. A gap at
32 position L would allow the magnetizable particles to become
33 released from the interior wall, though they would generally
34 remain localized. Thus, re-attraction by subsequent focusing
35 magnets 38 would not take an excessive amount of time.

36 Illustratively, in a first embodiment illustrated in
37 Fig. 2, the reaction vessels 12 containing the suspended

1 solid phase 14 are laterally translated along the magnet
2 array 16 by a linked conveyor belt 40 comprised of a sequence
3 of reaction vessel receptacles 42. A sequence of freely
4 rotatable rollers 44 are employed to provide support for the
5 conveyor belt 40. At least one such roller 46 is
6 mechanically connected to a motor 48, wherein the motor 48
7 rotates this roller 46, which in turn causes the conveyor
8 belt 40 and the reaction vessels 12 disposed therein to
9 translate relative to the magnet array 16.

10 The rear view of the magnet array in Fig. 3 illustrates
11 a first embodiment of a magnet array 16 support structure 50.

12 The magnet array 16 of Fig. 3 is a reverse view of the
13 magnet array 16 of Figs. 1A and 1B. The magnets of the array
14 are backed by a conductive material such as high-iron, low-
15 carbon steel to focus the magnetic field toward the reaction
16 vessels 12. The support structure 50, which attaches to the
17 magnet backing material, is preferably provided from a
18 magnetically non-reactive material such as aluminum or one of
19 its alloys to avoid unwanted disturbances in the magnetic
20 field established within the reaction vessels. The magnets
21 of the array 16 and the backing material are fastened to the
22 support structure 50 in a variety of ways, including via the
23 use of adhesive or mechanical fasteners. The support
24 structure 50 is itself suspended by being mechanically
25 attached to a wall of an enclosure (not illustrated), either
26 by adhesive, mechanical fasteners, or some combination
27 thereof.

28 In the illustrated embodiment of the support structure
29 in Fig. 3, the element is segmented into three portions: an
30 initial portion to the right of Fig. 3, a central portion,
31 and a small final portion on the left. The latter provides
32 support for the focusing magnets 24. In an alternative
33 embodiment, the central portion and the final portion are
34 combined, such that the support structure is formed of two
35 portions.

36 Fig. 3 also illustrates a rear view of the soft magnetic
37 insert 20. Disposed in a central location thereof is a

1 cross-section of a mechanical fastener 52 such as a screw
2 employed in securing the insert 20 to a wall of the
3 enclosure. In alternative embodiments, the soft magnetic
4 insert is supported by a respective support element such as a
5 stanchion or by an extension of the array magnet support
6 element 50. In the latter alternative, the support element
7 50 would then be one continuous element, if the final portion
8 and the central portion are continuous, or two elements if
9 the focusing magnets 24 is supported independently.

10 The orientation of wash solution nozzles as employed
11 along the magnet array 16 of the foregoing is illustrated in
12 Figs. 4A and 4B. In particular, a nozzle 30 such as that
13 used for reintroduction of wash solution at position F in
14 Figs. 1A or 1B is shown in cross-section in Fig. 4A. Solid
15 phase 14 has collected proximate the magnet array 16
16 (supported by the support element 50) at the rear of the
17 reaction vessel 12. The nozzle 30 is oriented with respect
18 to the reaction vessel 12 to provide a stream 60 of wash
19 solution from a wash solution reservoir 62 via a pump 64 to a
20 front, interior surface of the reaction vessel 12. This
21 avoids disturbing the solid phase collected at the rear of
22 the vessel 12.

23 In Fig. 4B, the orientation of a nozzle 32 such as that
24 used for resuspension wash at position H in Fig. 1B is
25 illustrated in Fig. 4B. A stream 66 of wash solution from
26 the reservoir 62 via the pump 64 is directed at the solid
27 phase previously collected proximate magnets in the array 16,
28 but now adjacent to the soft magnetic insert 20. The solid
29 phase is therefore not retained by magnets, and is easily
30 washed back into suspension by the stream 66 of wash solution
31 from the nozzle 32.

32 Having described preferred embodiments of the invention,
33 it will be apparent to those skilled in the art that other
34 embodiments incorporating the concepts may be used.

35 For instance, though the present invention has been
36 described in the context of a chemiluminescent immunoassay,
37 it can be applied to other assay environments in which the

1 separation of bound and unbound components by magnetic
2 separation is required. Further, the exact number of
3 positions in which magnetizable particles are exposed to
4 magnets 16 depends upon the exact nature of the desired
5 separation, the configuration of the magnets 16, the
6 characteristics of the magnetizable particles and the
7 associated bound component, etc.

8 Nozzle 32 has been shown in two locations in Figs. 1A
9 and 1B, specifically position H in Fig. 1A and position I in
10 Fig. 1B. While provided as one nozzle with a like reference
11 identifier in both figures, each embodiment of Fig. 1A and 1B
12 could be provided with a nozzle at position G for non-
13 resuspension wash, and another nozzle at position H for use
14 in an embodiment employing resuspension wash. Thus, the same
15 array configuration could be used for assays both employing
16 and not employing resuspension wash.

17 In addition to the illustrated embodiment of Fig. 2,
18 other means for translating the conveyor belt are envisioned,
19 such as a friction drive disposed on either side of the
20 conveyor at one or more positions.

21 In yet another embodiment of the present invention, the
22 reaction vessels 12 are translated along the magnet array 16
23 by way of a sequence of respective reaction vessel yokes (not
24 illustrated) connected to the respective reaction vessel near
25 the top of the vessel.

26 The arrangement of elements in Figs. 4A and 4B is a
27 generalized illustration of the relationship between the
28 elements, and is not intended to represent a preferred
29 layout. For instance, the nozzle 30, 32 in Figs. 4A and 4B
30 can also be located at the same relative position above a
31 respective reaction vessel 12, but angled in opposite
32 directions to properly direct the respective stream 60, 66.
33 Further, the pump and reservoir can be provided in a variety
34 of ways, as known to one skilled in the art.

35 The embodiments described in the foregoing are best
36 suited to particles and particle mixtures that relocate
37 easily within and along the wall of a reaction vessel in

1 response to changes in magnetic fields in the vicinity of the
2 reaction vessel. By "particle mixtures," it is meant
3 mixtures including magnetic particles, the sample, primary
4 reagents, ancillary reagents and wash solutions. Such easily
5 relocatable mixtures form consistently shaped and accurately
6 positioned pellets. Factors which contribute to the
7 responsiveness of mixtures to applied magnetic fields include
8 the size of the magnetic particles, the "stickiness" of
9 substances in the reaction mixture, the inclusion of
10 "slippery" surfactants in the reaction mixture, etc.

11 Assay mixtures which do not relocate easily or
12 consistently in response to moving magnetic fields tend to
13 form pellets of variable shapes in unpredictable locations,
14 particularly at positions N, O and P of Figs. 1A and 1B.
15 This inconsistency diminishes the benefit of shaping and
16 positioning the particle mass, since it introduces
17 variability in the resuspension step where the final reagent
18 is introduced. In addition, some assay mixtures tend to pack
19 the aggregate of particles more densely as the magnetic
20 forces shape and position them, thus frustrating efforts
21 taken to remove unbound label which might otherwise
22 improperly effect the desired reaction.

23 In general, it is desirable to minimize the number of
24 different wash steps in the separation and wash process;
25 additional process steps have the potential for introducing
26 variability. However, in certain assays, additional wash
27 steps are necessary to localize the magnetic particles into a
28 band on the side wall of a reaction vessel. Some assays
29 benefit significantly from a resuspension wash step.
30 Resuspension wash is used to wash out any unbound label that
31 may be trapped in the particle aggregate which would
32 otherwise contribute a non-specific signal to the true signal
33 at the assay read step. Therefore, as provided in the
34 previous embodiment, a further embodiment provides the
35 ability to selectively employ a resuspension wash, but with
36 an emphasis placed on minimizing unnecessary manipulation of
37 the particle aggregate.

1 Fig. 5A is an illustration of a system having a
2 continuous magnet array proximate a series of consecutive
3 reaction vessel positions. The array is comprised of
4 vertically oriented pairs of magnets 116, one above the
5 other, arranged such that the magnetic gradient generated by
6 the magnets at each reaction vessel position has a horizontal
7 maximum proximate the intersection of the two magnets. As in
8 the previously described embodiment, each reaction vessel, or
9 cuvette, 112 contains assay components and magnetizable
10 particles 114 which are initially in a freely distributed
11 state within the respective cuvette 112 (for instance, at
12 position A). The concentration of unbound solid phase
13 decreases as each cuvette traverses the magnet array (from
14 left to right in Figs. 5A and 5B).

15 For ease of reference, reaction vessel positions B
16 through G are referred to as an initial separation stage, at
17 which the solid phase is initially collected against the
18 interior wall of the cuvette, proximate the respective
19 magnets 116. One or more non-resuspension washes (discussed
20 subsequently) may be provided within the initial separation
21 stage. Position H is referred to as a resuspension wash
22 position, at which a resuspension wash may occur according to
23 the needs of each assay. Positions I through M are referred
24 to as a subsequent separation stage, even though in the case
25 of Fig. 5A, there is no resuspension wash and so the
26 separation begun in the initial separation stage is merely
27 continued. In the case of Fig. 5B, however, the subsequent
28 separation stage is utilized for the purpose of separating
29 the magnetic particles into a pellet against the cuvette
30 interior wall most proximate the magnet array. One or more
31 non-resuspension washes may occur within the subsequent
32 separation stage (discussed subsequently). Position N is
33 referred to as a final aspiration stage, where liquid phase
34 is removed from the cuvette prior to the final reagent
35 resuspension. Position O is an optional rest stage.
36 Position P is referred to as a final resuspension stage,
37 where a final reagent is introduced into the cuvette at such

1 an angle that the previously collected pellet 114 is washed
2 off the cuvette wall and is freely suspended in the reagent
3 solution.

4 As in Fig. 1A, optional non-resuspension wash positions
5 are provided at positions F, G and M. Here, liquid phase is
6 aspirated from the cuvette 112 via tubes 115, 117, 119, and
7 wash solution is introduced via nozzles 130, 132, 134. While
8 these nozzles are labeled "WASH BUFFER" in the figures, it is
9 understood that any wash solution desired may be dispensed
10 from the nozzles. Each of the washes at these positions is
11 optional. As in the prior embodiment, the nozzles may be
12 oriented in a variety of ways in order to avoid dislodging
13 the pellet of solid phase 114 collected at the respective
14 magnet 116; the goal is to remove liquid phase, then refill,
15 without disturbing the collected particles.

16 In Fig. 5A, a separation and wash process is illustrated
17 wherein resuspension wash is not used. Typically, the assay
18 will pass the resuspension wash position (position H in the
19 figures) with the reaction vessel being filled with wash
20 solution that was added either at position F or G. By
21 providing "full width" magnets, or magnets which extend
22 across the entire extent of the reaction vessel position, at
23 positions G and I, any tendency to split the particle band to
24 the left or right is reduced. Depending upon the response of
25 a particular reagent mixture to magnetic field manipulation,
26 this tendency may be evident with the trimmed magnets of the
27 foregoing embodiment.

28 For instance, certain "sticky" mixtures react to the
29 trimmed magnet at position G of Fig. 1A by accumulating on
30 the left side of the cuvette wall most proximate the magnets
31 (as viewed in Fig. 1A). This accumulation is maintained
32 through position H. Then, with the trimmed magnet at
33 position I, part of the magnetic particles break free of the
34 previous accumulation and gather on the right side, while
35 another part of the accumulation remains on the left side of
36 the cuvette wall. Since the nozzle 136 which dispenses the
37 final reagent at position P is preferably aimed at the middle

1 of the cuvette wall most proximate the magnets, this split
2 band of particles is not directly impinged by the final
3 reagent stream, and incomplete resuspension is achieved.

4 However, in the embodiment of Figs. 5A and 5B, full
5 width magnets at positions G and I avoid this split-banding,
6 and consequently result in more complete resuspension in the
7 final reaction mixture at position P.

8 Without resuspension wash at position H, the reduced
9 strength magnet at position H is strong enough to hold the
10 previously collected particle band 114 and prevent the
11 particles from being attracted to the stronger magnetic
12 forces at the neighboring positions, positions G and I, which
13 would otherwise result in split-banding.

14 The reduced strength magnet may be provided as a magnet
15 having dimensions similar to that of the remaining magnets of
16 the array but which provides a weaker magnetic field.
17 Alternatively, it may be preferred to provide a magnet
18 identical to the remaining magnets of the array, only
19 disposed further from the respective reaction vessel
20 position, such as by recessing the magnet, thus resulting in
21 a weaker effective magnetic field at the cuvette. See Fig. 6
22 for an illustration of a recessed magnet at position H.
23 Also, the material behind or around the magnet can be
24 utilized to impact the effective magnetic field strength that
25 acts on the particles to separate them from the solution and
26 hold them to the cuvette wall during washing. Further, the
27 reduced strength magnet may be implemented by recessing a
28 single magnet of the same strength as all other magnets of
29 the array, though all of the remaining reaction vessel
30 positions employ two magnets of opposing polarity. Thus, in
31 Figs. 5A and 5B, the magnet at position H appears to be half-
32 height with respect to the magnet pairs of the remaining
33 positions.

34 In Fig. 5B, the use of a resuspension wash in the
35 instant configuration is illustrated. Here, wash fluid is
36 aspirated out of the cuvette at position G but will not be
37 replaced there. Rather, the cuvette is moved to the

1 resuspension wash position, position H, without any liquid
2 phase in the cuvette. The resuspension wash nozzle 133 is
3 aimed at the particle aggregate on the "back" wall of the
4 cuvette, most proximate the magnets. Since the magnetic
5 forces holding the particles against the wall at this
6 position are of reduced strength, the force of the
7 resuspension wash stream is capable of resuspending much of
8 the particle aggregation. However, the particles will
9 immediately begin recollecting and will continue to do so at
10 the stepped down magnet positions which follow (i.e., at
11 positions I, J, K, ...). Any non-specific label that was
12 trapped in the aggregate will now be freed into the wash
13 solution and will be aspirated out of the reaction vessel at
14 either wash position M and/or N.

15 In either case, the magnet array of Figs. 5A and 5B
16 typically provides a particle aggregation of consistent shape
17 and position within the respective cuvette at the critical
18 final resuspension position, position P, regardless of the
19 characteristics of the contents of the assay mixture.

20 The tube 121 at position N of Figs. 5A and 5B is
21 employed to aspirate liquid phase from the respective cuvette
22 112 prior to the introduction, at position P, of the final
23 reagent via the nozzle 136. This reagent facilitates the
24 subsequent chemiluminescent reaction within a luminometer.
25 The reagent dispensing nozzle 136 at position P is preferably
26 angled towards the pellet 114 for maximum dispersion of the
27 accumulated particles.

28 In order to facilitate the complete dispersion of the
29 pellet 114 in the stream of final reagent at position P, the
30 respective magnet for that reaction vessel position, which
31 may be referred to as a "recollection" magnet, is preferably
32 positioned on the opposite side of the cuvette with respect
33 to all other reaction vessel positions, as shown in the top
34 view of Fig. 6. This "recollection" magnet is not shown in
35 Figs. 5A and 5B as it would otherwise obscure a portion of
36 the cuvette 112 at position P. The purpose of positioning
37 the magnet at this manner is to assist the stream of reagent

1 in releasing the pellet from the wall of the cuvette and to
2 aid in fully resuspending the magnetic particles in the final
3 reagent mixture. The cuvette does not remain at position P
4 long enough for the magnetic particles to begin re-
5 accumulating proximate this final, oppositely positioned
6 magnet to any significant degree. This is especially so
7 since reagent is being introduced into the cuvette for most
8 of the dwell time at this position.

9 In contrast to the system illustrated in Figs. 1A and
10 1B, the magnets at reaction vessel position I and subsequent
11 positions are disposed lower than the magnets at positions A
12 through G. The magnets at the start of the separation (the
13 initial separation stage) are positioned with respect to the
14 height of the cuvettes to accommodate a wide range of initial
15 reaction volumes. For example, if a high volume of liquid
16 phase is present in a cuvette, the magnetic forces as
17 provided by the embodiments of Figs. 5A and 5B are sufficient
18 to collect particles from the farthest distances in the
19 reaction fluid both above and below the magnetic centerline.
20 Once so collected, however, it is desirable to shift the
21 particle aggregation lower within the cuvette so that the
22 aggregate is positioned below the fluid level of the final
23 resuspension fluid volume. The lower magnets after this
24 step-down achieve the desired aggregate repositioning more
25 completely than the previous embodiment for certain reaction
26 mixtures. Since the resuspension wash volume does not
27 participate in the final reaction, being withdrawn at the
28 latest at position N, it can be selected such that the lower
29 set of magnets is capable of recollecting all particles,
30 including those in the upper portion of the resuspension wash
31 volume.

32 Assay mixtures which resist repositioning of the
33 particle mass tend to get even less responsive the longer
34 they are maintained in one location. Thus, delaying the
35 step-down to a later reaction vessel position within the
36 subsequent separation stage, such as at position K in Figs.
37 1A and 1B, only tends to make the aggregate more difficult to

1 accurately position. Locating the step-down immediately
2 following the resuspension wash position avoids this
3 difficulty.

4 These and other examples of the invention illustrated
5 above are intended by way of example and the actual scope of
6 the invention is to be determined from the following claims.

CLAIMS

What is claimed is:

- 1 1. A system, for use in an assay apparatus, for enabling:
2 separation and wash of magnetic particles in a reaction
3 vessel, said magnetic particles having sample components
4 bound thereto, the system comprising:
5 an array of plural, consecutive reaction vessel
6 positions, each position having a respective magnet adjacent
7 thereto, past which said reaction vessel transits in
8 sequence, said array comprising
9 an initial separation stage comprised of a first
10 consecutive plurality of said reaction vessel positions,
11 a resuspension wash position comprised of one of
12 said reaction vessel positions, adjacent said initial
13 separation stage,
14 a subsequent separation stage comprised of a
15 second consecutive plurality of said reaction vessel
16 positions, adjacent said resuspension wash position,
17 a final aspiration position comprised of one of
18 said reaction vessel positions, adjacent said subsequent
19 separation stage, and
20 a final resuspension position comprised of one of
21 said reaction vessel positions, adjacent said final
22 aspiration position;
23 an initial aspiration element, adjacent a first of said
24 reaction vessel positions of said initial separation stage,
25 adapted for selectively aspirating liquid phase from said
26 reaction vessel at said initial separation stage first
27 reaction vessel position;
28 a resuspension wash dispense element, adjacent said
29 resuspension wash position, adapted for selectively
30 dispensing resuspension wash solution into said reaction
31 vessel at said resuspension wash position;
32 a final aspiration element, adjacent a first reaction
33 vessel position of said subsequent separation stage, adapted
34 for selectively aspirating liquid phase from said reaction

35 vessel at said subsequent separation stage first reaction
36 vessel position; and
37 a reagent dispense element, adjacent said final
38 resuspension position, adapted for selectively dispensing
39 reagent into said reaction vessel at said final resuspension
40 position to resuspend said magnetic particles in said
41 reagent,
42 wherein said array is configured such that said
43 reaction vessel transits, in sequential order, said initial
44 separation stage, said resuspension wash position, said
45 subsequent separation stage, said final aspiration position,
46 and said final resuspension position,
47 wherein said magnet adjacent said resuspension wash
48 position is of reduced magnetic strength relative to all
49 other magnets adjacent said array of plural consecutive
50 reaction vessel positions.

1 2. The system of claim 1, wherein each magnet of said
2 initial separation stage, said subsequent separation stage,
3 and said final aspiration position provides a magnetic field
4 which tends to attract said magnetic particles into a
5 substantially horizontal cluster on an interior wall of said
6 reaction vessel most proximate said magnet.

1 3. The system of claim 2, wherein said magnets adjacent
2 said subsequent separation stage, said final aspiration
3 position, and said final resuspension position are disposed
4 such that said substantially horizontal cluster develops at
5 a point, on said interior wall of said reaction vessel most
6 proximate said magnet, below a point where said
7 substantially horizontal cluster develops at said initial
8 separation stage.

1 4. The system of claim 1, further comprising at least one
2 rest position intermediate said final aspiration position
3 and said final resuspension position past which said
4 reaction vessel transits in sequence.

1 5. A method of separating and selectively washing magnetic
2 particles within a reaction vessel, said magnetic particles
3 having sample components bound thereto, the method
4 comprising the steps of:

5 passing said reaction vessel through an array of
6 reaction vessel positions of an assay apparatus, comprising
7 an initial separation stage, a resuspension wash position, a
8 subsequent separation stage, a final aspiration position,
9 and a final resuspension position, for separating said
10 magnetic particles from a liquid phase in said reaction
11 vessel and washing said magnetic particles free of unbound
12 sample components, wherein:

13 said initial separation stage comprises a first
14 consecutive plurality of said reaction vessel positions and
15 an initial aspiration element, adjacent a first of said
16 reaction vessel positions of said initial separation stage,
17 adapted for selectively aspirating liquid phase from said
18 reaction vessel at said initial separation stage first
19 reaction vessel position;

20 said resuspension wash position comprised of one of
21 said reaction vessel positions, adjacent said initial
22 separation stage, and a resuspension wash dispense element,
23 adjacent said resuspension wash position, adapted for
24 selectively dispensing resuspension wash solution into said
25 reaction vessel at said resuspension wash position;

26 said subsequent separation stage comprised of a second
27 consecutive plurality of said reaction vessel positions,
28 adjacent said resuspension wash position;

29 a final aspiration position comprised of one of said
30 reaction vessel positions, adjacent said subsequent
31 separation stage, and a final aspiration element, adjacent a
32 first reaction vessel position of said subsequent separation
33 stage, adapted for selectively aspirating liquid phase from
34 said reaction vessel at said subsequent separation stage
35 first reaction vessel position; and

36 a final resuspension position comprised of one of said
37 reaction vessel positions, adjacent said final aspiration
38 position, and a reagent dispense element, adjacent said
39 final resuspension position, adapted for selectively
40 dispensing reagent into said reaction vessel at said final
41 resuspension position to resuspend said magnetic particles
42 in said reagent,
43 wherein said array is configured such that said
44 reaction vessel transits, in sequential order, said initial
45 separation stage, said resuspension wash position, said
46 subsequent separation stage, said final aspiration position,
47 and said final resuspension position, and
48 wherein said magnet adjacent said resuspension wash
49 position is of reduced magnetic strength relative to all
50 other magnets adjacent said array of plural consecutive
51 reaction vessel positions.

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FIG. 1A

WITHOUT RESUSPENSION WASH

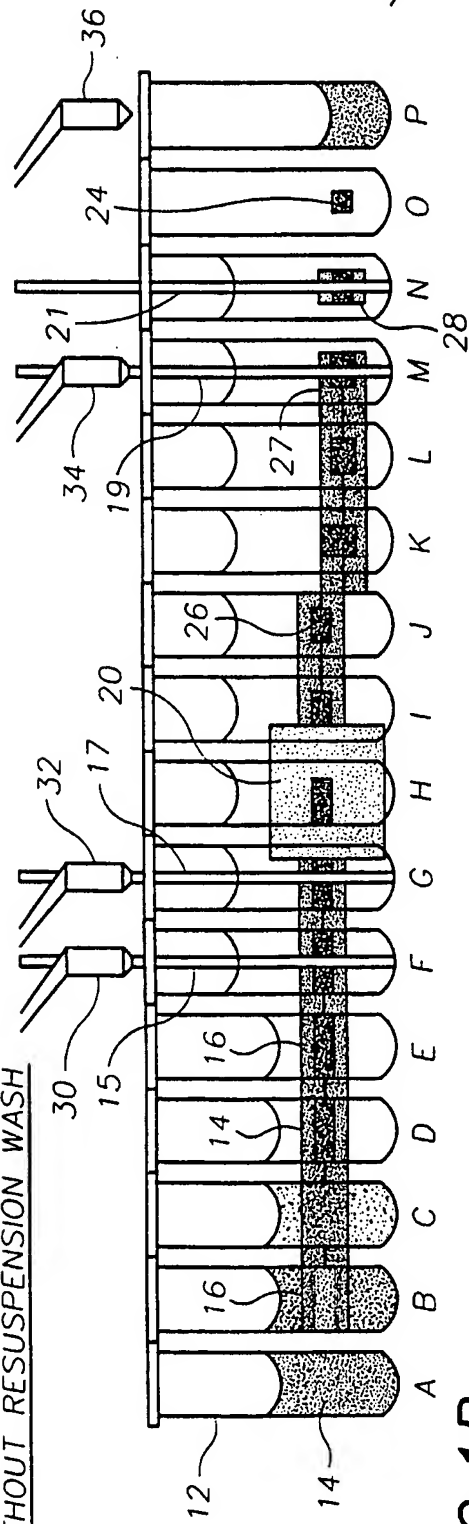


FIG. 1B

WITH RESUSPENSION WASH

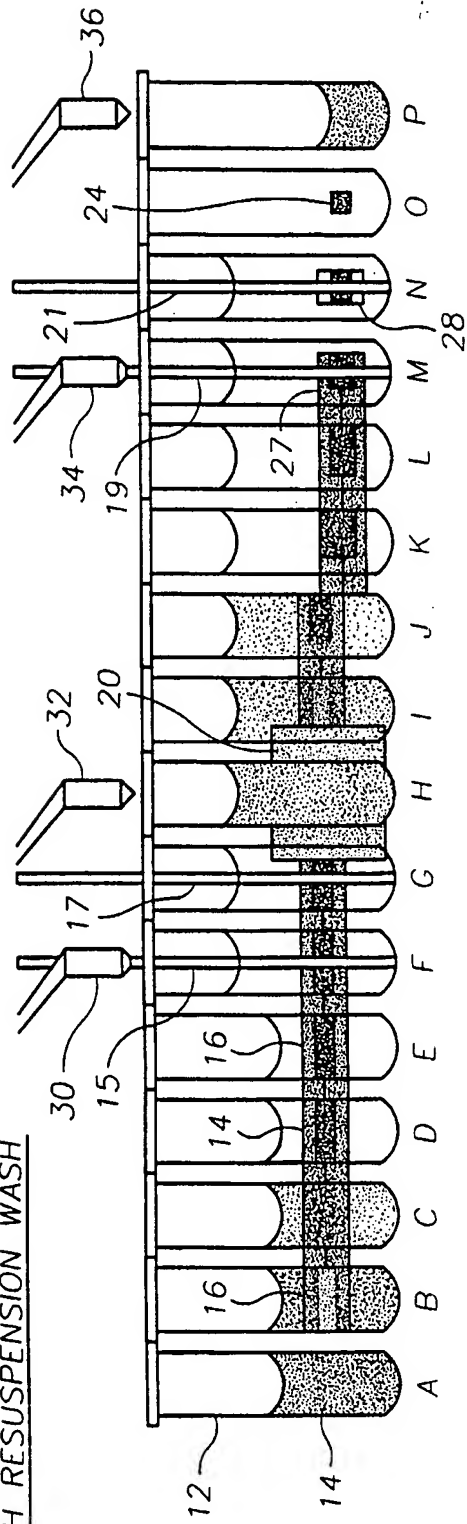


FIG. 2

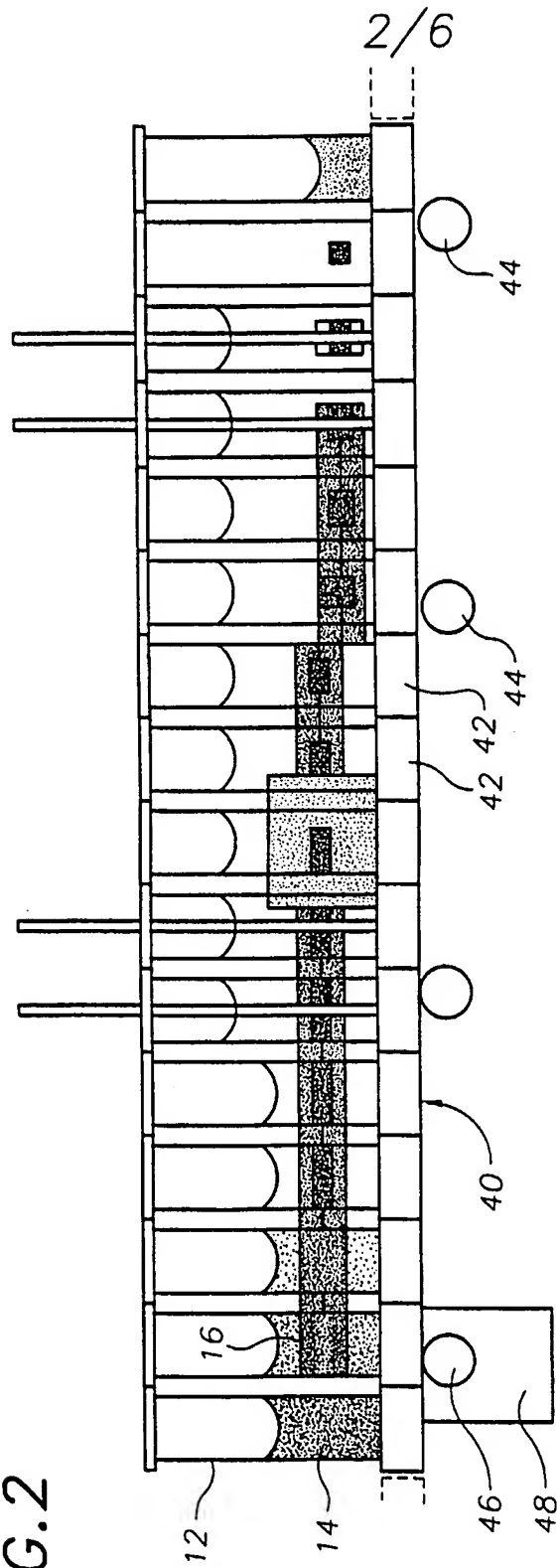
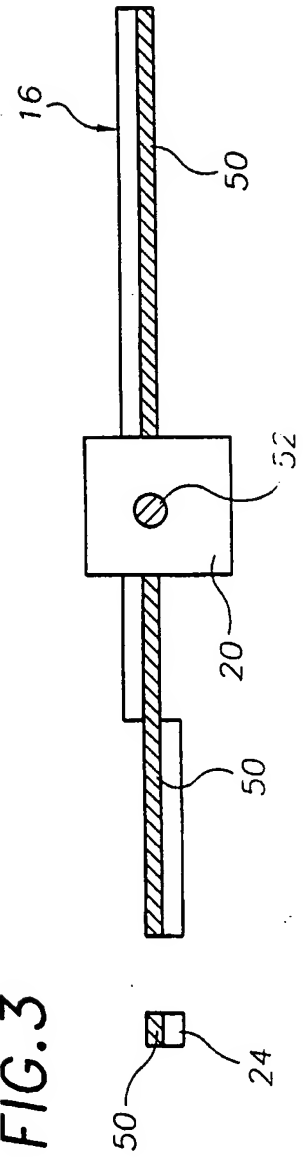


FIG. 3



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FIG. 4B

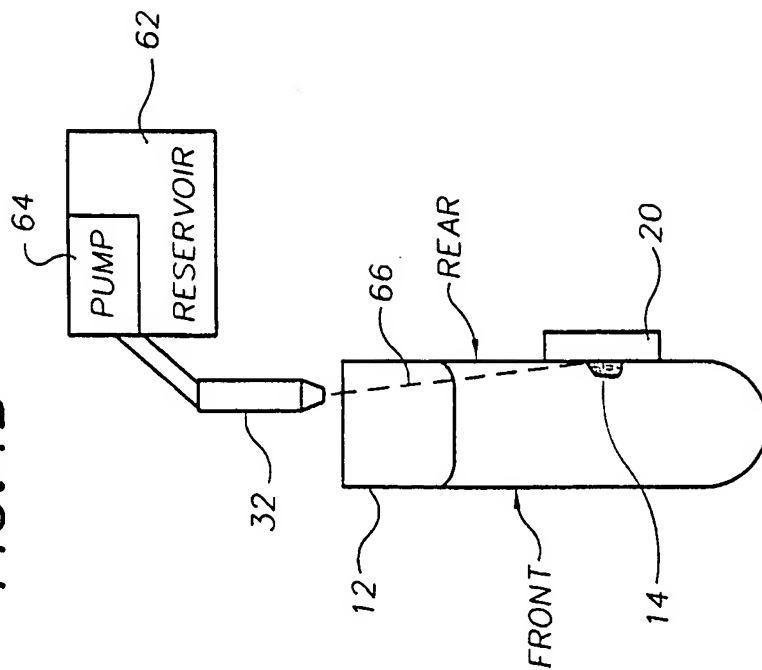
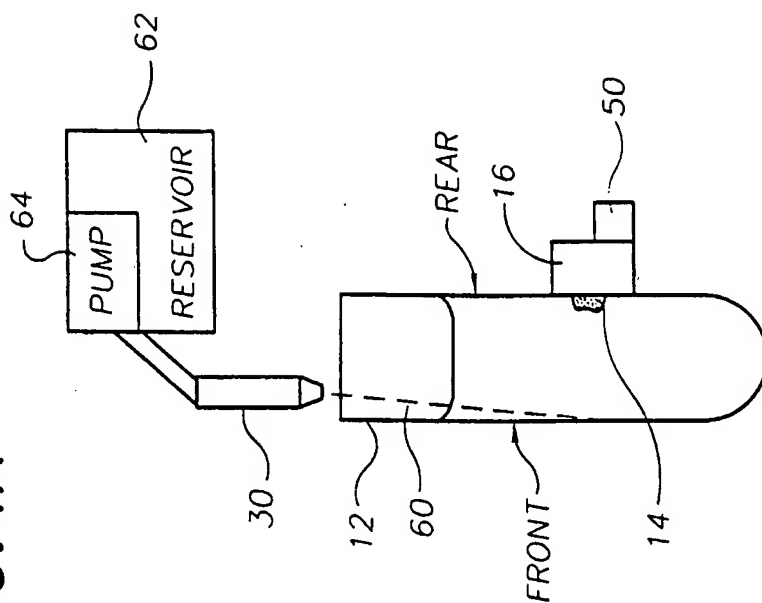
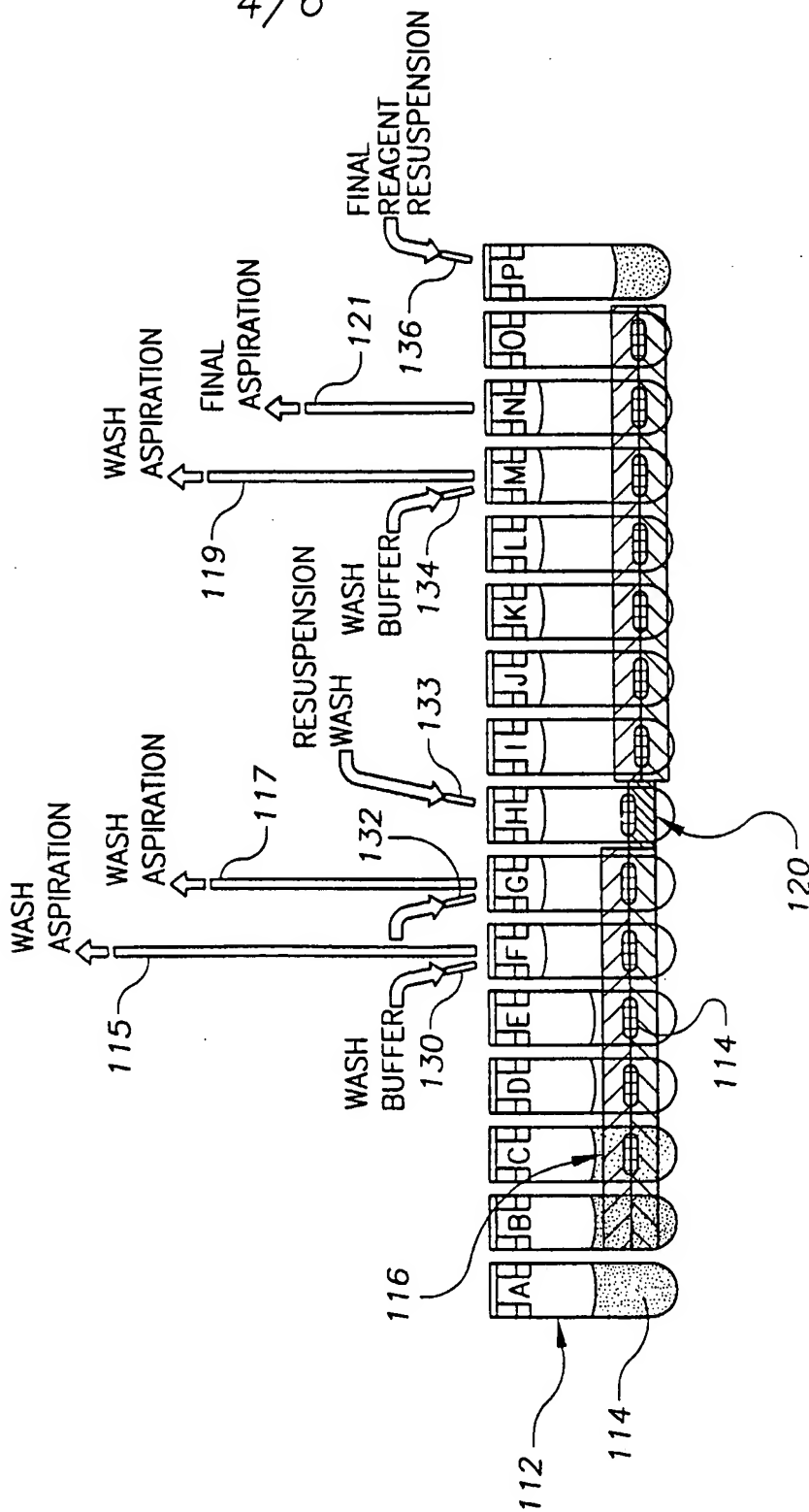


FIG. 4A



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FIG. 5A
WITHOUT RESUSPENSION WASH



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FIG. 5B
WITH RESUSPENSION WASH

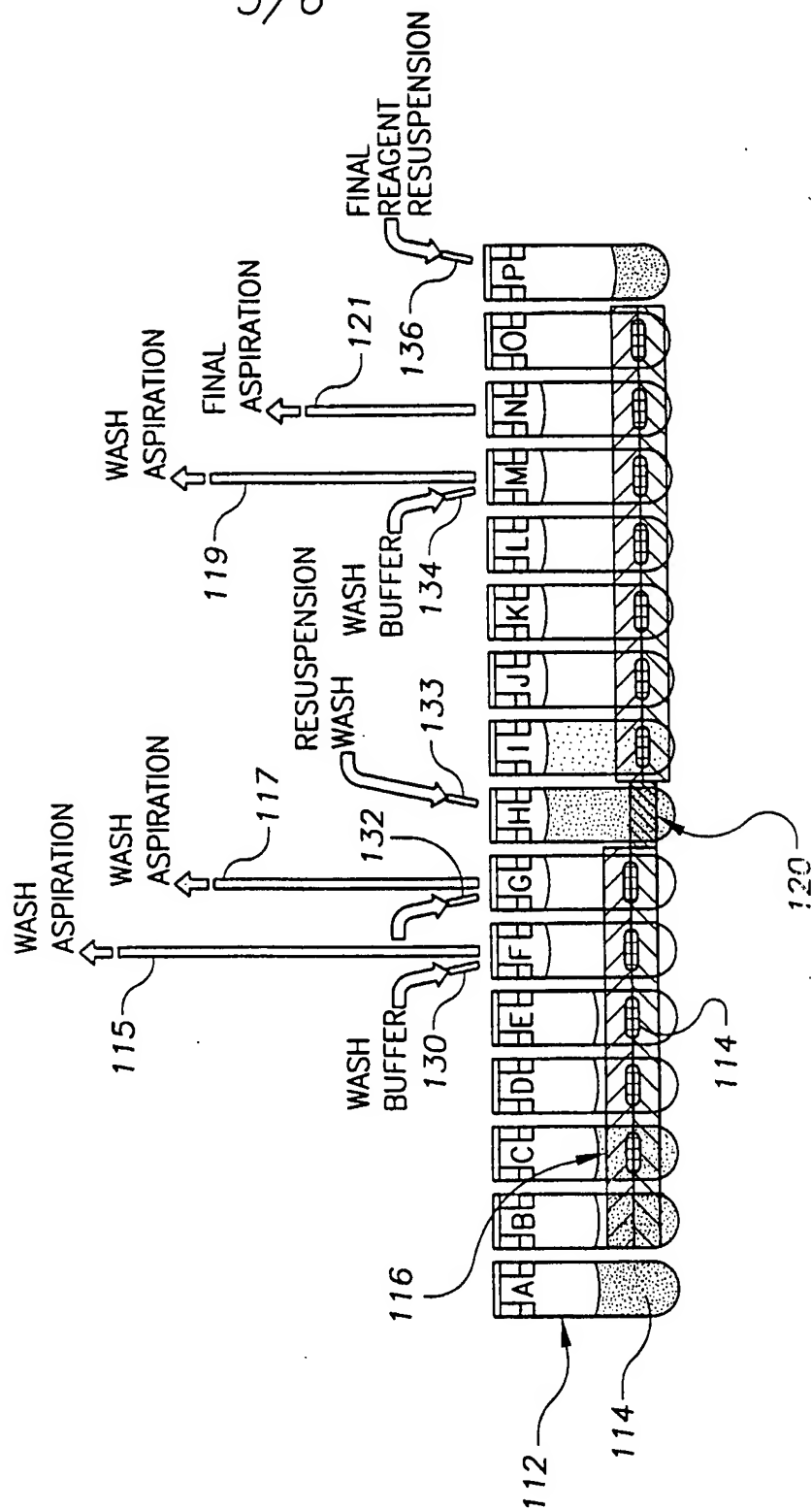
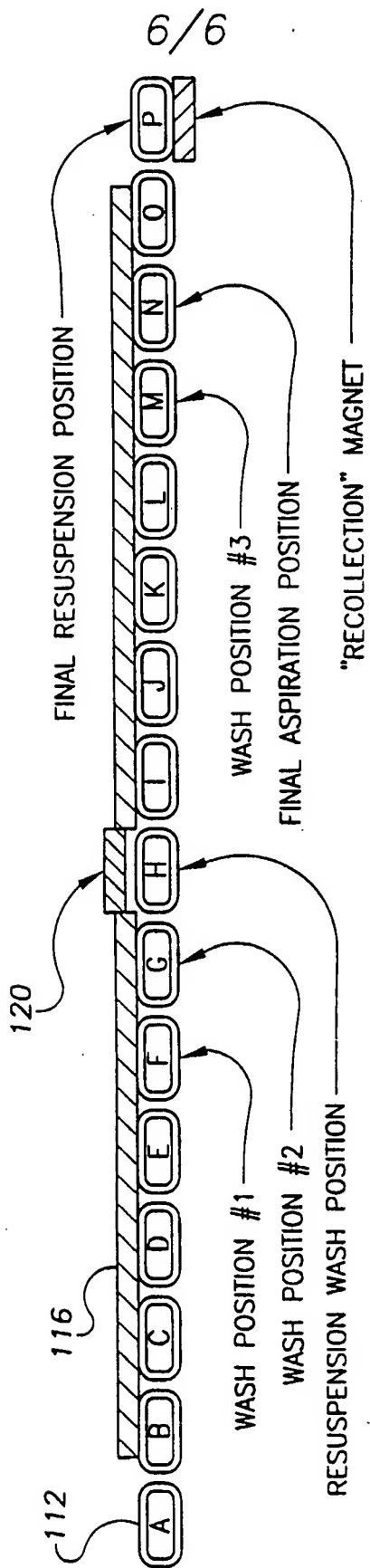


FIG. 6



INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 99/01646

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N35/00 B03C1/28 G01N33/543

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N B03C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 806 665 A (CHIRON DIAGNOSTICS CORP) 12 November 1997 (1997-11-12) cited in the application column 7, line 10 -column 8, line 12; figures 3,4 ---	1-5
A	EP 0 502 638 A (CIBA CORNING DIAGNOSTICS CORP) 9 September 1992 (1992-09-09) page 26, line 45 -page 27, line 18; figures 21B,34,35 ---	1,5
A	WO 91 09308 A (HOLMES MICHAEL JOHN ;DIATEC INSTR AS (NO)) 27 June 1991 (1991-06-27) page 2, line 7 -page 3, line 6 --- -/--	1,5

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

13 December 1999

Date of mailing of the international search report

20/12/1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB 99/01646

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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